1. NAME OF THE MEDICINAL PRODUCT

Strefen Honey and Lemon Flavour 8.75mg/dose oromucosal spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One actuation contains 2.92 mg of Flurbiprofen, three actuations equal to one dose contains 8.75mg, corresponding to 16.2 mg/ml Flurbiprofen.

Excipients with known effect:
Methyl parahydroxybenzoate (E218) 1.181 mg/dose
Propyl parahydroxybenzoate (E216) 0.23624 mg/dose
Fragrances containing allergens (in Lemon Flavour and Honey Flavour)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oromucosal spray, solution

Clear, colourless to slightly yellow solution with a taste of honey and lemon.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Strefen Honey and Lemon Flavour is indicated for the short-term symptomatic relief of acute sore throat and associated symptoms such as difficulty in swallowing, swollen throat, acute cough, throat tickle and clearing and post-nasal drip in adults.

4.2 Posology and method of administration

Posology

For short term use only.
Adults aged 18 years and over:
One dose (3 actuations) administered to the back of the throat every 3-6 hours as required, up to a maximum of 5 doses in a 24 hour period.

Paediatric population
The safety and efficacy of Strefen Honey and Lemon Flavour in children or adolescents under 18 years has not been established.

Elderly patients
A general dose recommendation cannot be given, since to date clinical experience is limited. The elderly are at increased risk of the serious consequences of adverse reactions.

The lowest effective dose should be administered for the shortest duration necessary to control symptoms (see section 4.4).

Method of Administration

For oromucosal administration.

Do not inhale whilst spraying.

It is recommended that this product should be used for a maximum of three days.

Before first use, activate the pump by pointing the nozzle away from you and spraying a minimum of four times until a fine, consistent mist is produced. The pump is then primed and ready for use.
Between each dose point the nozzle away from you and spray a minimum of once ensuring a fine, consistent mist is produced. Always ensure a fine consistent mist is produced before dosing the product.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Patients who have previously shown hypersensitivity reactions (e.g asthma, bronchospasm, rhinitis, angioedema or urticaria) in response to acetylsalicylic acid or other NSAIDs.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration) and intestinal ulceration.
- History of gastrointestinal bleeding or perforation, severe colitis, haemorrhagic or haematopoietic disorders related to previous NSAID therapy.
- Last trimester of pregnancy (See section 4.6)
- Severe heart failure, severe renal failure or severe hepatic failure (see section 4.4).
- Children and adolescents below 18 years.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

<u>Infections</u>

Since in isolated cases an exacerbation of infective inflammations (e.g. development of necrotising fasciitis) has been described in temporal association with the use of systemic NSAIDs as a class, the patient is advised to consult a physician immediately if signs of a bacterial infection occur or worsen during the flurbiprofen spray therapy. It should be considered whether initiation of an anti-infective antibiotic therapy is indicated.

In cases of purulent bacterial pharyngitis/tonsillitis, the patient is advised to consult a physician as the treatment needs to be re-evaluated.

Masking of symptoms of underlying infections:
Epidemiological studies suggest that systemic non-steroidal anti-inflammatory drugs (NSAIDs) can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Strefen Honey and Lemon Flavour 8.75mg/dose oromucosal spray is administered while the patient suffers from fever or pain in relation to infection, monitoring of infection is advised.

Treatment should be administered for three days maximum.

If the symptoms get worse or if new symptoms occur, the treatment should be re-evaluated.

If mouth irritation occurs, flurbiprofen treatment should be withdrawn.

Elderly population

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory

Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease. Flurbiprofen spray should be used with caution in these patients.

Other NSAIDs

The use of flurbiprofen spray with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Systemic lupus erythematosus and mixed connective tissue disease

Patients with systemic lupus erythematosus and mixed connective tissue disease may have an increased risk of aseptic meningitis (see section 4.8), however this effect is not usually seen with short term limited use products such as flurbiprofen spray.

Cardiovascular, Renal and Hepatic Impairment

NSAIDs have been reported to cause nephrotoxicity in various forms including interstitial nephritis, nephrotic syndrome and renal failure. The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly, however, this effect is not usually seen with short term, limited use products such as flurbiprofen spray.

Hepatic

Mild to moderate hepatic dysfunction (see sections 4.3 and 4.8).

Cardiovascular and cerebrovascular effects

Caution (talk with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs, (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for flurbiprofen when given at a daily dose of no more than 5 doses (3 sprays per dose).

Nervous System effects

Analgesic induced headache - In the event of prolonged use of analgesics or use beyond the regulations headache may occur, which must not be treated with increased doses of the medicinal product.

Gastrointestinal

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly, however this effect is not usually seen with short term limited use products such as flurbiprofen spray. Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) to their healthcare professional.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants

such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

If GI bleeding or ulceration occurs in patients receiving flurbiprofen, the treatment should be withdrawn.

Haematological effects

Flurbiprofen, like other NSAIDs, may inhibit platelet aggregation and prolong bleeding time. Flurbiprofen spray should be used with caution in patients with a potential for abnormal bleeding.

Dermatological

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Flurbiprofen spray should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

This product contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Fragrances containing allergens

This medicine contains fragrance with Anisyl Alcohol, Citral, Citronellol, d-Limonene, Geraniol and Linalool.

Anisyl Alcohol, Citral, Citronellol, d-Limonene, Geraniol and Linalool may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Flurbiprofen should be avoided in combination with:	
Other NSAIDS including cyclooxygenase-2 selective inhibitors:	Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (esp. gastrointestinal adverse events such as ulcers and bleeding), (see section 4.4).
Acetylsalicylic acid (low dose)	Unless low-dose aspirin (not above 75mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (see section 4.4).

Flurbiprofen should be used with <u>caution</u> in combination with:	
Anticoagulants:	NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).
Anti-platelet Agents	Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
Antihypertensive drugs (Diuretics, ACE inhibitors, angiotensin-II-antagonists):	NSAIDs may reduce the effect of diuretics and other antihypertensive drugs may enhance nephrotoxicity caused by inhibition of cyclooxygenase, especially in patients with compromised renal function
Alcohol	May increase the risk of adverse reactions, especially of bleeding in the gastrointestinal tract
Cardiac glycosides:	NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels - adequate control and, if necessary, dose adjustment is recommended
Ciclosporin:	Increased risk of nephrotoxicity.
Corticosteroids:	Increased risk of gastrointestinal ulceration or bleeding (see section 4.4)
Lithium:	May increase serum levels of lithium – adequate control and, if necessary, dose adjustment is recommended
Methotrexate:	The administration of NSAIDs within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.
Mifepristone:	NSAIDs should not be used for 8 – 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
Oral antidiabetics	Alteration of blood glucose levels reported (increased check rate recommended)
Phenytoin	May increase serum levels of phenytoin – adequate control and, if necessary, dose adjustment is recommended
Potassium sparing diuretics	Concomitant use may cause hyperkalaemia
Probenecid Sulfinpyrazone	Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of flurbiprofen.
Quinolone antibiotics	Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
Selective serotonin reuptake inhibitors (SSRI's)	Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
Tacrolimus:	Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
Zidovudine:	Increased risk of haematological toxicity when NSAIDs are given with zidovudine.

<u>Paediatric population</u>

No additional information available.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, flurbiprofen should not be given.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose

- the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);

- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

- the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.

- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, flurbiprofen is contraindicated during the third trimester of pregnancy (see section 4.3).

Breastfeeding

In limited studies, flurbiprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely. However, because of possible adverse effects of NSAIDs on breast-fed infants, flurbiprofen spray is not recommended for use in nursing mothers.

Fertility

There is some evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
Dizziness, drowsiness and visual disturbances are possible undesirable side effects after taking NSAIDs. If affected, the patient should not drive or operate machinery.

4.8 Undesirable effects

Hypersensitivity reactions to NSAIDs have been reported and these may consist of:

(a) Non-specific allergic reactions and anaphylaxis

(b) Respiratory tract reactivity, e.g. asthma, aggravated asthma, bronchospasm, dyspnoea

(c) Various skin reactions, e.g. pruritus, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. There is insufficient data to exclude such a risk for flurbiprofen oromucusal spray, solution.

The following list of adverse effects relates to those experienced with flurbiprofen at OTC doses for short-term use.

(Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10000 to <1/1000), Very rare (<1/10000), not known (cannot be estimated from the available data))

Blood and lymphatic system disorders:

Not known: anaemia, thrombocytopenia.

Cardiac and vascular disorders:

Not known: Oedema, hypertension, cardiac failure

Nervous System disorders:

Common: dizziness, headache, parasthesia

Uncommon: somnolence

Respiratory, thoracic and mediastinal disorders:

Common: throat irritation

Uncommon: exacerbation of asthma and bronchospasm, dyspnoea, wheezing, oropharyngeal blistering, pharyngeal hypoaesthesia.

Gastrointestinal disorders:

Common: diarrhoea, mouth ulceration, nausea, oral pain, paraesthesia oral, oropharyngeal pain, oral discomfort (warm or burning feeling or tingling of the mouth).

Uncommon: abdominal distension, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, glossodynia, dysgeusia, oral dysaesthesia, vomiting

Skin and subcutaneous tissue disorders:

Uncommon: various skin rashes, pruritus.

Not known: severe forms of skin reaction such as bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

General disorders and administration site conditions:

Uncommon: pyrexia, pain

Immune System disorders:

Rare: anaphylactic reaction

Psychiatric disorders:

Uncommon: insomnia

Hepatobiliary disorders:

Not known: hepatitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the risk/benefit balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache, and gastrointestinal bleeding are also possible. In more serious poisoning with NSAIDs, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation, blurred vision and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning with NSAIDs metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Management

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal and if necessary correction of serum electrolytes if the patient presents within one hour of ingestion or a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma. There is no specific antidote to flurbiprofen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Throat preparations, other throat preparations.

ATC Code: R02AX01

Flurbiprofen is a propionic acid derivative NSAID which acts through inhibition of prostaglandin synthesis. In humans flurbiprofen has potent analgesic, antipyretic and anti-inflammatory properties and the 8.75 mg dose dissolved in artificial saliva has been shown to reduce prostaglandin synthesis in cultured human respiratory cells. According to studies using the whole blood assay, flurbiprofen is a mixed COX-1/COX-2 inhibitor with some selectivity towards COX-1.

Pre-clinical studies suggest that the R (-) enantiomer of flurbiprofen and related NSAIDs may act on the central nervous system; the suggested mechanism is by inhibition of induced COX-2 at the level of the spinal cord.

Flurbiprofen from the 8.75 mg spray has been shown to penetrate into the layers of the whole human pharynx tissue including the deeper layer in an ex vivo model.

A single dose of flurbiprofen 8.75 mg delivered locally to the throat as three sprays has been demonstrated to relieve sore throat, including swollen and inflamed sore throats through a significant change in the severity of throat soreness area under the change (AUC) from baseline curve (mean difference (standard deviation)) for active treatment versus placebo from 0 to 2 hours (-1.82 (1.35) vs -1.13 (1.14)), 0 to 3 hours (-2.01 (1.405) vs -1.31 (1.233)) and 0 to 6 hours (-2.14 (1.551) vs -1.50 (1.385). Significant differences in the AUC from baseline curve from 0 – 6 hours compared to placebo were also seen for other qualities of sore throat including pain intensity (-22.50 (17.894) vs -15.64 (16.413)), difficulty swallowing (-22.50 (18.260) vs -16.01 (15.451)), swollen throat (-20.97 (18.897) vs -13.80 (15.565)) and sore throat pain relief (3.24 (1.456) vs 2.47 (1.248)). The change from baseline at individual time points across the different qualities of sore throat demonstrated significance starting from 5 minutes and lasting for up to 6 hours.

Flurbiprofen 8.75 mg spray has been shown to be non-inferior to the lozenge based on AUCs for pain intensity difference from baseline to 2 hours post dose. Similar non-inferiority was observed with associated symptoms such as difficulty in swallowing [spray (-36.46) vs lozenge (-35.91)] and swollen throat [(Spray (-30.63) vs lozenge (-29.19)]. Meaningful absence of other associated symptoms like acute cough [spray (85%) vs and lozenge (54%)], post-nasal drip [spray (70%) vs lozenge (59%)], throat tickle [spray (60%) vs lozenge (43%)] and throat clearing [spray (37%) vs lozenge (32%)].

For those patients taking antibiotics for Strep infection, there was statistically significant greater relief of sore throat pain intensity for flurbiprofen 8.75 mg lozenge from 7 hours and onwards after antibiotics were taken. The analgesic effect of flurbiprofen 8.75 mg lozenge was not reduced by the administration of antibiotics to treat patients with streptococcal sore throat.

Multiple-dose efficacy over 3 days has also been demonstrated.

Paediatric Population

No specific studies in children have been undertaken with Strepfen Honey and Lemon. Efficacy and safety studies on flurbiprofen 8.75 mg lozenges have included children aged 12 – 17 years, although small sample size means that no statistical conclusions can be drawn.

5.2 Pharmacokinetic properties

Absorption

A single dose of flurbiprofen 8.75 mg is delivered directly to the throat as three sprays and the flurbiprofen is readily absorbed, with detection in the blood between 2 and 5 minutes and plasma concentrations peaking at 30 minutes after administration, but remaining at a mean low level of 1.6 µg/mL which is approximately 4 times lower than a 50 mg tablet dose. Strepfen Honey and Lemon demonstrates bioequivalence to flurbiprofen 8.75 mg lozenge. Absorption of flurbiprofen can occur from the buccal cavity by passive diffusion. Rate of absorption is dependent on pharmaceutical form with peak concentrations achieved more rapidly than, but of similar magnitude to, those achieved after an equivalent swallowed dose.

Distribution
Flurbiprofen is rapidly distributed throughout the body and is extensively bound to plasma proteins.

Biotransformation / Elimination
Flurbiprofen is mainly metabolised by hydroxylation and excreted via the kidneys. It has an elimination half-life of 3 to 6 hours. Flurbiprofen is excreted in very small amounts in human milk (less than 0.05 µg/ml). Approximately 20-25% of a flurbiprofen oral dose is excreted unchanged.

Special Groups
No difference in pharmacokinetic parameters between elderly and young adult volunteers has been reported following oral administration of flurbiprofen tablets. No pharmacokinetic data have been generated in children below 12 years of age following administration of Flurbiprofen 8.75 mg however administration of both flurbiprofen syrup and suppository formulations indicate no significant differences in pharmacokinetic parameters compared with adults.

5.3 Preclinical safety data

There are no preclinical data of relevance additional to information already included in Sections 4.4, 4.6 and 4.8

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex
Disodium phosphate dodecahydrate
Citric acid monohydrate
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Sodium hydroxide
Honey flavour
Lemon flavour
N,2,3-Trimethyl-2-isopropylbutanamide
Saccharin sodium (E954)
Hydroxypropylbetadex
Purified water

Qualitative composition of Honey flavour:
Flavouring substance(s)
Flavouring preparation(s)
Propylene glycol (E1520)

Qualitative composition of Lemon flavour:
Flavouring substance(s)
Flavouring preparation(s)
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After first opening:
6 months

6.4 Special precautions for storage

Do not refrigerate or freeze

6.5 Nature and contents of container

A white opaque HDPE bottle with a multi-component pump unit and protective polypropylene overcap. The pump is comprised of polyoxymethylene, low density polyethylene, high density polyethylene, polypropylene, stainless steel and PIB Compound (Polyisobutylene – Rubber).

Pack size: Each bottle contains 15 ml of solution which provides approx. 83 actuations

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Reckitt Benckiser Healthcare (UK) Limited
103-105 Bath Road
Slough
SL1 3UH
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8 MARKETING AUTHORISATION NUMBER(S)

PL 00063/0763

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10/10/2025